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Double Blind Control Study of Antihypertensive Agents

II. Further Report on the Comparative Effectiveness of Reserpine, Reserpine and Hydralazine, and Three Ganglion Blocking Agents, Chlorisondamine, Mecamylamine, and Pentolinium Tartrate

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COOPERATIVE STUDY ON
ANTIHYPERTENSIVE AGENTS*
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This report presents the results after one year of follow-up of 759 hypertensive patients who were begun on one of a number of randomized, double blind treatment regimens using various antihypertensive agents. The plan of the study and the methods of procedure have been published previously.[1]

In brief, only patients whose diastolic blood pressure levels averaged 90 mm. Hg or above from the fourth through the sixth hospital days were included in the study. These patients were divided into categories of "mild, moderate, and severe" on the basis of the scores obtained in 5 panels: basal diastolic pressure, optic fundi, and abnormalities of the cardiac, renal, and central nervous systems.

Treatment for patients in the mild and half of the moderately severe group consisted of 1 of 3 possible regimens as follows: (1) reserpine 0.5 mg. twice daily for 2 weeks followed by 0.25 mg. twice daily thereafter plus hydralazine 25 mg. 4 times daily for 2 weeks followed by 50 mg. 4 times daily thereafter, (2) reserpine as above plus placebo of hydralazine as above, and (3) placebo of reserpine plus placebo of hydralazine. Assignment of a given regimen to an individual patient was carried using a double blind, randomization technique.[1] Each regimen was continued unchanged for one year except for death, default, or other special reasons described below.

Treatment for the remaining half of the moderately severe cases and for all of the severe group consisted of reserpine in the dosages stated above plus 1 of 3 ganglion blocking agents: mecamylamine, chlorisondamine, or pentolinium. The blocking agents were specially prepared in approximately equipotent tablets so that titration of dosage could be carried out in each case without revealing the identity of the particular ganglion blocking drug being administered.

In addition to determining clinic recordings of blood pressure, each patient was given a blood pressure apparatus for twice daily measurements in the

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Complete tabular data will be included in the reprints.

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These included the following Veterans Administration Hospitals: Brooklyn; Chicago West Side; Iowa City; Oklahoma City; Richmond, Va.; San Juan, P.R.; Seattle, and Washington, D.C.

home. Follow-up reports were summarized every 3 months, and a complete examination including laboratory studies was carried out at the end of 1 year of follow-up.

Results

1. *Loss of Patients from Given Treatment Regimen.*—Of the 759 patients who were begun on one of the randomized regimens, 426 were treated without change of therapy for the full year.

Of the 333 lost to the study, 155, or 47% (20% of the total started), were patients who did not return or could not or would not cooperate. The majority of these dropped out in the first 2 months of treatment. Such losses are inevitable when an effort is made to avoid selection, since a number of deteriorated, alcoholic, or uncooperative individuals will be included. The drop-outs were greater in large cities, Brooklyn, Chicago, Washington, than in a primarily rural area (Iowa City).

When the losses were classified according to treatment regimen there were no great differences between the various groups. The percentage lost ranged from 37% in the reserpine-hydralazine group to 54% in the chlorisondamine-treated patients. The reasons for the losses, however, varied in incidence in the different treatment categories. For example, 40 or 64% of the 62 losses in the hydralazine-reserpine group were due to failure of the patient to return or to lack of cooperation as compared to only 17, or 37%, of the 46 losses in the placebo group.

The difference is probably explained by the higher incidence of side-effects on the former treatment regimen. The losses due to failure to return or to lack of cooperation also was high (61%) in the cases treated with reserpine.

Losses due to poor cooperation were lower in the patients treated with ganglion blocking agents, ranging from 32% of the total losses of patients taking mecamylamine to 41% in the case of pentolinium. Nevertheless, the incidence of reported side-effects was high in the patients treated with ganglion blocking drugs. The reason for the smaller percentage of voluntary drop-outs in the latter treatment groups may be due to the fact that the patients tended to have more severe and symptomatic disease and, hence, were more willing to tolerate side-effects.

Deaths: Since all deaths among veterans are reported routinely to Veterans Administration Central Office, a complete follow-up as to mortality was obtained. Death accounted for 14% of the losses (6% of the total started) during the first year of treatment. As would be expected because of the increased severity of disease the percentage dying was higher in the patients treated with blocking agents than in the groups on the other regimens. The causes of death were as follows: renal failure 11, cerebrovascular accident 7, myocardial infarction 6, congestive heart failure 2, sudden death 5, unknown 4, and 1 each from ruptured duodenal ulcer, dissecting aneurysm, acute alcoholism, and postoperative complications.

Major Side-Effects: Of the losses, 9% were due to side-effects which were sufficiently troublesome to warrant discontinuation of therapy. The incidence was 15% of the losses in patients taking reserpine plus hydralazine, 6% in those receiving reserpine alone, and 2% in the placebo-treated group. It is probable that losses due to this cause in the groups receiving active agents were in reality higher than reported, since some of those who failed to return may have done so because of side-effects. Somewhat fewer of the patients receiving pentolinium tartrate were lost because of side-effects than in those receiving mecamylamine or chlorisondamine. Further data on these cases are presented below in the section on side-effects.

Treatment Failures: Of the losses, 12% were due to failure of the regimens to prevent severe elevations of blood pressure or other menacing complications such as hypertensive encephalopathy. The criteria for discontinuing the double blind regimens were as follows: (1) home diastolic average 130 mm. Hg or about for 3 weeks or longer confirmed by clinic readings; (2) home diastolic average 140 or above for 1 week or longer; (3) evidence of *serious* organic progression such as an attack of acute hypertensive encepha-

lopathy (accompanied by high diastolic pressures), advancing congestive heart failure despite digitalis and periodic diuretics, development of hemorrhages, exudates, and/or papilledema in the optic fundi.

The incidence of treatment failure was highest in the placebo group (26%) and lowest in the patients treated with reserpine plus hydralazine (2%). The most common complication necessitating a change in therapy was resistant congestive heart failure. In addition there were 3 cases of cerebrovascular accident and myocardial infarction in which a change in treatment was considered necessary.

II. *Antihypertensive Effectiveness.*—Unless stated to the contrary, the average blood pressure levels reported in a post-treatment period represent the average for 3-month periods of twice daily recordings of blood pressure taken by each patient or a member of his family in the home. The pretreatment control values are based on the averages of recordings taken 4 times daily in the hospital ward from the fourth through the sixth days of hospitalization.[1]

In general, the patients who did not complete the full year exhibited a lesser antihypertensive response than those who did. This was probably due to the fact that treatment failures and deaths were included in the former group. Post-treatment data for those patients lost during the first 2 months of treatment are not included despite the fact that nearly 50% of all losses occurred during that interval. The reason for not including them is that the results were considered to be untrustworthy, since they were constituted predominantly from the uncooperative patients who failed to return for follow-up; nor does it seem of great practical importance to know which regimen was more effective for patients who would not accept treatment. Their prevalence in this study varied between 13% and 27% among the various regimens.

Average Changes in Blood Pressure on Various Regimens: Since the post-treatment averages were essentially unchanged from quarter to quarter the third month results were used; this included all patients (most treatment failures and deaths) except those who dropped out before completion of the first quarter.

The results are similar in most respects to those reported previously in a smaller series of cases.[1] Reserpine was slightly superior to placebos producing an average reduction of 3/5.1 mm. Hg (systolic/diastolic) as compared to an average elevation of 3.7/2.0 mm. Hg in the placebo-treated group. Reserpine plus hydralazine resulted in an average fall of 4.9/10.5 mm. Hg.

The results after the 3 ganglion blocking agents did not differ greatly one from the other. In the 88 patients who received mecamylamine, the reduction of blood pressure averaged 16.3/14.1 mm. Hg, in 91 patients given chlorisondamine it was 15.2/12.3, and in 65 given pentolinium tartrate the reduction averaged 15.4/13.4 mm. Hg. In the moderate group of hypertensive patients the average reduction was approximately 11/10 mm. Hg in each of the 3 regimens. In the severe group the reductions were greater, averaging approximately 24/20 mm. Hg. Whereas reserpine plus hydralazine affected diastolic blood pressure primarily, reserpine plus ganglion blocking agents affected systolic slightly more than diastolic pressure. If the reductions of blood pressure seem rather small for all regimens, it should be remembered that "basal" hospital blood pressures were used as the pretreatment control values. "Casual" pretreatment blood pressures probably would average considerably higher.

Percentage Distribution of Response on Various Regimens: Distributions of the per cent of patients with indicated amounts of blood pressure change are shown in Figures 1 through 4. Figure 2 indicates the percentage distribution of changes in diastolic pressure in the patients taking reserpine, hydralazine, or their placebos. A reduction of 5 mm. Hg or more was obtained in 70% of the patients taking reserpine plus hydralazine, 54% of those on reserpine alone, and 33% of the placebo group. The placebo group displays a nearly normal distribution curve for diastolic blood pressure with a mean close to zero change in blood pressure. Corre-

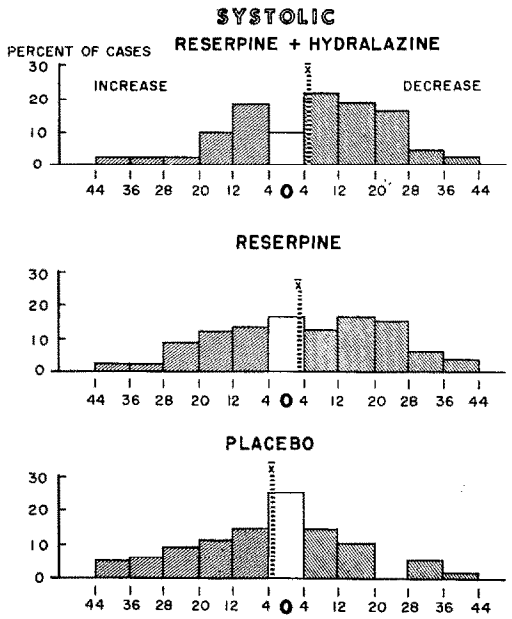

Fig. 1.—Percentage distributions of systolic pressure responses with the reserpine-hydralazine (above), the reserpine-placebo (middle), and the placebo-placebo regimens. Per cent of patients is indicated on the ordinate and change in systolic pressure on the abscissa with decrease of pressure plotted to the right.

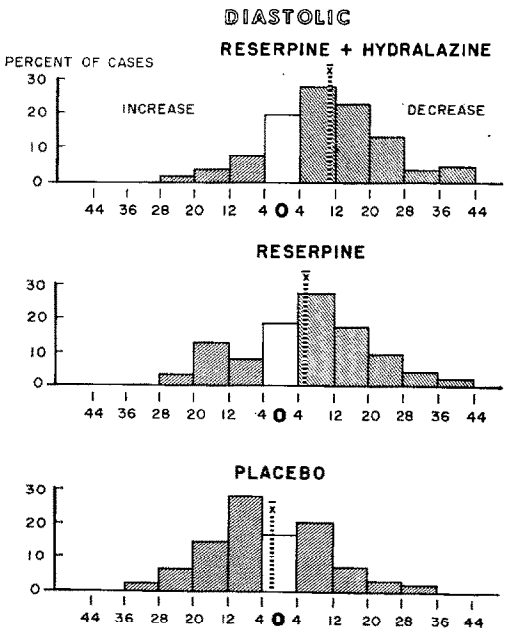

Fig. 2.—Percentage distributions of diastolic pressure responses. Other notations as in Figure 1.

sponding data for the ganglion blocking drugs shown in Figure 4 indicated that 69% to 77% of the patients exhibited a fall of 5 mm. or more in diastolic blood pressure. The distribution of both systolic and diastolic pressure as shown in Figures 3 and 4 is quite similar comparing one blocking agent with the others. The wide distribution of systolic pressure shows the great variability of re-

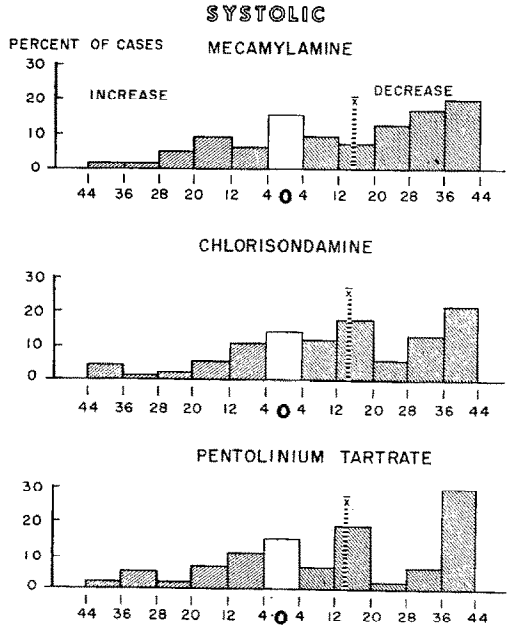

Fig. 3.—Percentage distributions of systolic pressure responses of patients taking 1 of the 3 ganglion blocking agents plus reserpine.

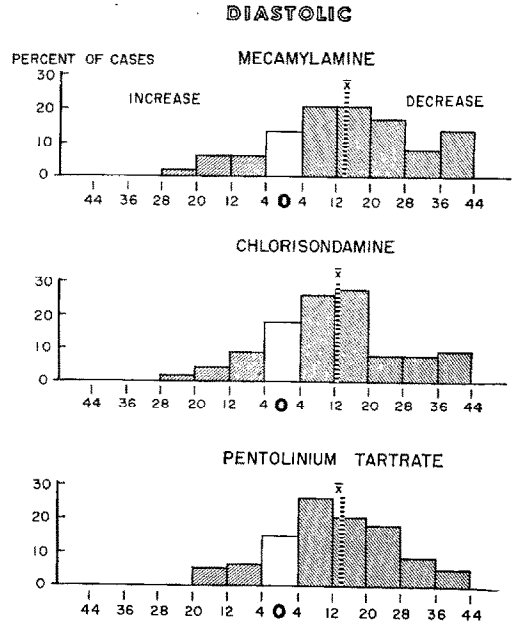

Fig. 4.—Percentage distributions of diastolic pressure of same patients as in Figure 3.

sponse to all of the ganglion blocking drugs (Fig. 3).

Differences Between Hospitals: Tabulation of the data by individual hospitals disclosed that results usually were comparable within the various institutions. The hospitals which treated more Negroes reported higher average blood pressures under treatment for patients on all agents including placebos. There were no hospitals where one blocking agent appeared more effective than the others. In one hospital, reserpine alone was as effective as reserpine plus hydralazine, but there were only 12 patients on each of these regimens.

Effects of Age and Race: With almost all regimens the average reduction in systolic blood pressure was greater in patients under as compared to those over 50 years of age. There were no other significant differences. Similar comparisons were made between Negro and Caucasian patients. No significant differences were observed. Negroes appeared to show no response to reserpine, but the elevation with placebos was greater so that the difference between the reserpine and placebo groups was about the same in Negroes as in Caucasians.

Influence of Pretreatment Level of Blood Pressure: The degree of change in diastolic blood pressure also was analyzed in regard to the level of pretreatment blood pressure and severity score for the various regimens. The results indicated that regardless of the antihypertensive agent used, the average reduction in diastolic pressure was greater in the patients with high initial pressures. The higher the pretreatment pressure, the greater was the potential fall. It is probable that greater reductions of blood pressure could have been achieved by more aggressive dosage with the ganglion blocking drugs in patients with the lowest initial diastolic blood pressure. The average daily dose in the moderately severe group was about half that administered to the patients with severe hypertension. The reductions of blood pressure were more than twice as great in the severe group. It would appear that when the choice of the dose is left to the discretion of the clinic physician, he will treat most aggressively the patients with the highest blood pressure levels.

Home Versus Clinic Levels of Blood Pressure: The averages of blood pressure levels recorded after a 15-minute rest period in the clinic [1] were consistently higher than the averages of recordings made at home. This held true for all regimens including placebos. The relative antihypertensive effectiveness of one regimen as compared to another was about the same whether home or clinic blood pressure averages were used for determining the results. Since the home recordings represent a far greater number of readings (twice daily) and since the average home recordings in the placebo group were much closer to the average of the pretreatment hospital recordings, they probably reflect more accurately the general levels of blood pressure during the treatment period than do the clinic readings.

Stability of Average Blood Pressures: The average of home recordings in a given patient usually varied little from one quarter to another. There often was, however, considerable variation from one home recording to the next or from one clinic reading to the next. Thus, the blood pressures of the hypertensive patients seemed to fluctuate more or less widely about a mean, the average generally being fairly stable although subject to change depending on the treatment regimen imposed. Although generally fairly stable, the averages for individuals usually were not as constant as the averages for groups of individuals. The variation of group average blood pressure from one quarterly period as compared to the other quarters never exceeded 4 mm. Hg systolic or 3 mm. Hg diastolic in any of the treatment groups.

Effects on Organic Changes: A preliminary analysis of the effects of treatment on organic changes was attempted in the patients who completed 1 year of treatment. These patients were subdivided into 4 groups according to height of initial blood pressure and then further divided as to whether they did or did not obtain a significant reduction of blood pressure. The average severity

scores in the fundic, cardiac, central nervous system, and renal panels as well as their totals were then compared before and after 1 year of treatment.

This method of lumping severity scores into averages is inadequate, since it makes the incorrect assumption that 2 grades of 2 equals 1 of Grade 4. For a preliminary survey of directional changes, however, it offered a convenient method of comparison with the understanding that the table should be interpreted only in the most general terms. In all groups there was a decrease in severity scores. For example, in the group treated with placebos the cardiac and central nervous system panel averages showed significant improvement at the end of 1 year, and even the renal panel was slightly improved.

Some of this apparent evidence of improvement might be accounted for by the fact that data only on the patients treated throughout the year on the same regimen were tabulated. Thus, the unfavorable cases of patients who died or became treatment failures were not included. Since the incidence of treatment failures was higher in the groups who did not show a significant reduction of blood pressure, the bias introduced would tend to favor these subdivisions, particularly the placebo group. With the possible exception of the patients with initial diastolic pressure levels above 120 mm. Hg the percentage improvement in total panel scores did not indicate significant differences after 1 year between those whose pressures were reduced and those exhibiting no reduction. A longer period of follow-up will be required, however, before any judgment can be made as to the effects of antihypertensive drugs on the progression of organic disease.

III. *Side-Effects.*—Major Side-Effects: A further breakdown of the major reactions in which the side-effects were judged to be sufficiently troublesome to warrant change of treatment is as follows: Of the 9 cases in the hydralazine-reserpine group there were 2 instances of depression, 1 of sleep disturbance with severe nightmares, 1 of edema of the hands and feet; 1 complained of impotence, 1 of severe headaches, 1 of nausea and dizziness, 1 exhibited butterfly erythema, but without other evidences of lupus, and 1 had a gastrointestinal hemorrhage of undetermined cause. Not all of these reactions can be ascribed definitely to drug effects. More appeared to be those associated with reserpine than with hydralazine. In the 4 cases taking reserpine alone, treatment was discontinued in 2 because of depression and in the other 2 because of impotence. The latter cases are of interest, since reserpine generally is not believed to have effects on sexual function. Treatment was discontinued in one case taking placebos because of a generalized dermatitis.

Treatment was changed because of side-effects in 5 patients receiving mecamylamine. The reactions consisted of 1 each of the following disturbances: orthostatic hypotension, dizziness and constipation, paralytic ileus, impotence and gastrointestinal complaints, and upper abdominal pain with vomiting. In 10 patients receiving chlorisondamine, orthostatic hypotension accounted for 3 losses, difficult voiding for 1, abdominal pain for 1, diarrhea for 1, and multiple complaints for 4. Treatment was discontinued in the pentolinium group because of orthostatic hypotension in 1 and multiple complaints in 1.

Minor Side-Effects: An attempt was made to determine the incidence of minor side-effects by a questionnaire-interview method.[1] Each patient was interviewed by the clinic secretary or physician at regular intervals. The interview was made from a check list containing standard questions relating to side-effects generally believed to be associated with the agents under study.

Unfortunately, the interviews carried out prior to treatment revealed a high incidence of the side-effects usually attributed to reserpine and hydralazine. For most of the side-effects the changes from the pretreatment incidence were insignificant at both 1 month and 1 year after treatment and also during the intervening quarterly periods. Headaches decreased in the drug-treated and placebo groups. The incidence of nasal stuffiness increased in the patients receiving reserpine either alone or with hydralazine as compared

to the placebo group. Increased appetite was noted in the reserpine-treated groups but was equally prominent in the placebo-treated patients. For the remaining side-effects of joint pains (hydralazine), lethargy and fatigue, depressed feeling, and nightmares (reserpine), there were no significant changes after as compared to before treatment in either the drug-treated or placebo groups. The number of patients failing to return because of side-effects was, of course, unknown.

Side-effects related to the gastrointestinal tract were common after the ganglion blocking drugs, the frequency of complaints being definitely higher during treatment than before. As compared to the pretreatment period the incidence of constipation increased after treatment by 21% to 36%, depending on the blocking agent. Other gastrointestinal side-effects including bloating, distention, and anorexia were increased by 16% to 40% and dryness of the mouth by 14% to 27%. The incidence of orthostatic faintness was not increased in the period between 1 and 12 months after beginning treatment but may have been higher in the earlier period of dosage regulation. Complaints of impairment of visual accommodation increased after treatment especially in the patients taking chlorisondamine where 19% were required to wear dark glasses when exposed to bright sunlight. Difficult voiding appeared to be an uncommon side-effect.

Comment

The results of the present study confirm in general the previous preliminary report.[1] It was not possible from the preliminary results in a smaller series of patients to determine whether reserpine exerted a significant antihypertensive effect as compared to placebo. The more extensive data reported here indicate that oral reserpine does have an antihypertensive effect, although it is not very great.

The constancy of results obtained from the first 3-month period to the next for each of the regimens used indicated that 3 months was a sufficient period for the evaluation of antihypertensive effectiveness of these particular agents. Such a short period, however, may not reveal chronic toxicity.

The double blind method as employed here did not appear to be a sensitive method for detecting minor side-effects. Part of the difficulty may be due to the fact that side-effects were reported at 1 month and then quarterly when most of the acute disturbances such as headache and palpitation from hydralazine, and constipation and dry mouth, etc., from the ganglion blocking drugs had abated. In addition, some of the early drop-outs may have occurred because of side-effects which, of course, would not be reported. In the pretreatment period, the high incidence of complaints similar to the expected side-effects indicates the need for caution in interpreting the true prevalence of minor side-reactions in studies when such pretreatment evaluations have not been made.

It is of interest that in patients with moderate hypertension, reserpine plus hydralazine resulted in a slightly greater reduction in diastolic pressure than that produced by reserpine plus ganglion blocking agents, although the latter produced a slightly greater fall in systolic pressure. As mentioned previously, the reduction of blood pressure in the patients treated with ganglion blocking agents might have been greater if more aggressive dosage had been employed. On the other hand, the participating physicians were experienced in the use of these agents and administered doses which resulted in a significant incidence of the side-effects associated with ganglionic blockade. The reserpine and hydralazine regimen employed an uncomplicated, fixed dose schedule; side-effects ascribable to drug action were lower than in the patients treated with ganglion blocking agents, and hydralazine toxicity was not a prominent feature with the doses of the drug employed in this study. These considerations favor the use of reserpine plus hydralazine over ganglion blocking drugs in the management of patients with moderately severe hypertension, at least as an initial trial before resorting to the blocking agents.

Summary

Various antihypertensive agents were administered using a randomized double blind technique to male patients with elevations of basal diastolic pressure above 90 mm. Hg with the following results.

Of 759 patients entering the study, 426 completed one year of treatment. Of the losses, 47% were due to failure to return or to lack of cooperation, the majority occurring within the first 2 months of treatment. Deaths accounted for 14% of the losses, severe elevation of blood pressure or acute hypertensive complications for 12%, and side-reactions for 9%.

The average blood pressures in the various treatment groups remained essentially unchanged from the third month to the end of the year.

In 86 patients with "mild" and "moderate" hypertension receiving placebos, there was a slight elevation of blood pressure averaging 3.7/2.0 mm. Hg. In 136 similar patients given reserpine in a maintenance dose of 0.5 mg. daily, there was a slight reduction averaging 3.0/5.4 mm. Hg. In 139 patients given the same amount of reserpine plus hydralazine in a maintenance dose of 200 mg. per day, the average reduction of blood pressure was 4.9/10.5 mm. Hg.

Reserpine 0.5 mg. daily plus 1 of 3 ganglion blocking agents—mecamylamine, chlorisondamine or pentolinium—was tested in treatment groups each comprising 65 to 91 "severe" and "moderately severe" hypertensive patients. The antihypertensive effects of the 3 ganglion blocking agents were essentially similar, averaging approximately 15.5/13 mm. Hg.

With all of the antihypertensive regimens, the higher the pretreatment level of blood pressure, the greater was the degree of fall. Age or race did not seem to influence antihypertensive effectiveness significantly.

In general, inter-regimen differences were similar in each of the participating hospitals.

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